

1 the *Pseudomonas cepacia* microorganism problem?

2 A Yes, it brought the project to a screeching halt for a
3 while.

4 Q Can you tell the Court what you mean by screeching
5 halt?

6 A Yeah. At the time we had already submitted a product
7 license application to the regulatory authority in the UK and
8 I was engaged in transferring the process of manufacture of
9 that formulation to our factory in Liverpool and at the same
10 time was directing what we term an in-use test. This is a
11 test where we simulate how the patient would use the product.
12 So that involved taking the top off the bottle, pouring out
13 two five-mil spoons, night and morning, for I think about
14 three weeks, just to see how the product would behave when
15 used by a patient. It's standard practice to make absolutely
16 certain there won't be any surprises when the most important
17 person comes to use that product. And during that exercise
18 we analyzed the contents of the bottle at the end to check
19 that there had been no changes, no significant changes in
20 content.

21 And it was during that period at the end of that
22 test that we had a remarkable finding, and that was that one
23 of the parabens had dramatically decreased in concentration
24 in a period of about three weeks and it was dramatic in that
25 we had other data from sealed bottles where there had been

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1 little change in a period of two years. So something
2 mysterious had happened.

3 Q In addition to the drop in one of the parabens, was the
4 *Pseudomonas cepacia* contamination problem manifested in any
5 other way?

6 A Yes. Yes, we had an intense period of hypothesis as to
7 how could this happen because it didn't fit any known laws of
8 degradation of the parabens, and I sat and I puzzled and I
9 held the bottle, looked at it and thought, and then I was
10 looking inside the cap and I could see a black mark and
11 instinctively I smelled the cap and there was a strong smell
12 of spoilage. Then I thought perhaps we had probably a
13 microorganism here. I immediately contacted our
14 microbiologists and there was an investigation and that's
15 where we found over a million organisms of *Pseudomonas*
16 *cepacia* in each mil of syrup.

17 Q This discovery of the microorganism, the *Pseudomonas*
18 *cepacia* problem that occurred in the first half of 1985; is
19 that correct?

20 A First half, probably June and earlier.

21 Q You were research leader at that point, correct?

22 A Yes.

23 Q And did your responsibilities as research leader
24 include trying to develop an improved antimicrobial
25 preservative system for the Zantac Syrup to overcome this

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1 *Pseudomonas cepacia* problem?

2 A What it did, I had only recently taken on the project
3 and submitted reports to the regulatory submission. I was
4 research leader responsible for the project. I had seen the
5 results of the low preservative content. I had spotted this
6 micro problem by looking at the cap and I felt intimately
7 involved in this problem. It was clearly on my plate.

8 Q Could you turn your attention to plaintiffs' trial
9 exhibit 239, please?

10 (Pause for document examination.)

11 Q Could you identify this document, Dr. Long?

12 A Yes. This is a memorandum faxed across to a colleague
13 based in the States at Glaxo, Inc., informing him of the
14 problem that we had just discovered with the microorganism.
15 The reason I was telling Mr. Chitniss this is that he in
16 parallel was setting up or about to set up stability programs
17 for this inadequately, programs for this inadequately
18 preserved formulation. I immediately wanted to stop him
19 wasting his time. It's another indication of how many
20 parties were involved in this dramatic event which stopped
21 the development.

22 Q So this appearance of this bug brought development work
23 on both sides of the Atlantic to a screeching halt; is that
24 correct?

25 A It did that and it also posed questions about what

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1 would we do with the submission which we had already provided
2 to the authority in the UK, how to handle that.

3 Q Reading from the first paragraph of your July 25, 1985
4 memorandum, quote, as a result of a recent in-use test on
5 Zantac Syrup in which we found there was a significant loss
6 of propylparaben due to microbial contamination, the
7 development program of this syrup has been delayed pending
8 further investigation. End quote. Does that accurately
9 reflect your assessment of the problem?

10 A Yes, it does.

11 Q Returning to the time line July 1985, does this
12 memorandum reflect that event depicted on trial exhibit 116?

13 A I'll have to look at it in the file. I can't quite
14 read that. 116?

15 Q Yes.

16 A Could you give me the question again?

17 Q I jumped ahead. The November 1983 to July 1985 states
18 on trial exhibit 116, quote, further work revealed that,
19 although Glaxo's original ranitidine syrup formulation met
20 the requirements of the Antimicrobial Preservative
21 Effectiveness test of the USP, it supported the growth of a
22 water-borne bacterium known as *Pseudomonas cepacia*. It's
23 referencing trial exhibit 64. Your testimony thus far is
24 coinciding with this event and this memorandum; is that
25 correct?

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1 A That's correct, yes.

2 Q Dr. Long, did you solve the problem posed by
3 *Pseudomonas cepacia* with respect to the Zantac Syrup?

4 A Yes. There was a period of intense thinking,
5 speculation, what preservatives could we use, considered a
6 whole range, and then looked, considered all the criteria
7 that we would need to consider in selecting a preservative,
8 an additional preservative. As a result of that ethanol was
9 one of the candidates.

10 Q What amount of the alcohol did you ultimately settle
11 upon to solve this problem posed by the *Pseudomonas cepacia*?

12 A We ultimately settled on 7.5 percent weighted body.

13 Q Did that addition of that amount of alcohol work to
14 solve the problem. Did it eradicate the contamination?

15 A Yes, it did.

16 Q I direct your attention to plaintiffs' trial exhibit
17 245. I note for the Court this is an excerpt of Glaxo's
18 April 1986 amendment to its initial new drug application for
19 Zantac Syrup in the United States. I direct your attention
20 to Y72, Y072400. That's plaintiffs' trial exhibit 245.

21 Dr. Long, having reviewed this and based on your
22 knowledge, do you confirm in this text Glaxo is advising the
23 Food and Drug Administration of its modified syrup
24 formulation containing the alcohol?

25 A Yes. This page describes the background and what the

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1 formulations of Zantac Syrup reflected in Table D8.1?

2 A Yes.

3 Q Directing your attention to Y060620, could you turn to
4 that page and take a minute to review it, Doctor?

5 (Pause for document examination.)

6 A Yes. The crux of this page is that we have predicted a
7 shelf-life of 18 months when stored at 2 to 30 degrees
8 centigrade and that the addition of ethanol does not
9 adversely affect the stability of the ranitidine.

10 Q Glaxo wasn't claiming any shelf-life extension or
11 stability enhancements of the alcohol-containing formulation
12 at this time?

13 A At that time, no. I was pleased there was no adverse
14 effect because that is what I was looking for.

15 Q That was a concern at that point in time, that the
16 addition of alcohol to the syrup formulation might actually
17 impact stability in a negative way; is that correct?

18 A That's correct. In any formulation, in my experience,
19 if we had an extra ingredient it increases the risk of some
20 sort of interaction. There are already eleven ingredients in
21 the syrup, we have added a twelfth. It's quite an exquisite
22 cocktail potential for interactions.

23 THE COURT: It had nothing to do with the ethanol
24 itself so much but a general concern over --

25 THE WITNESS: A general concern just adding another

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1 the '249 patent.

2 Q Was there ever any question in your mind that you were
3 the inventor of the '249 patent?

4 A No, there wasn't, in that if I go back to the history
5 of what was happening at that time, as I described yesterday,
6 we had first of all a problem that I lost the parabens
7 preservative and then I immediately wanted to know why was
8 this happening, where had it gone, what was the cause of this
9 mystery. Then I, the breakthrough was when I saw this, as I
10 described yesterday, a cap with a black mark and the strange
11 smell and I instigated the investigation with a
12 microbiological colleague, found the organism, *Pseudomonas*
13 *cepacia*, so I got the problem, identified the cause of the
14 problem. And then I was the team leader at that time, the
15 ball was firmly in my court, I wanted to find the solution to
16 cure this problem and in order to do that I looked at the
17 options. It was me that went through how are we going to get
18 over this problem and it was me that came up with the idea
19 that we should use alcohol, amongst other things, to test to
20 see whether we could overcome the problem. I firmly believe
21 I am the inventor, it's mine.

22 Q Could you describe for the Court the work that is
23 reflected on the second page of Trial Exhibit 242? I believe
24 the date is August 16, 1985; is that correct?

25 A That's correct. This is a summary on that date of the

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